

# The Clinical Practice Guideline on diagnosis and treatment of hyponatraemia: a response from Otsuka Pharmaceutical Europe Ltd

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The publication of the guideline by the European Renal Best Practice (ERBP) group has helped stimulate a debate on this important cause of morbidity and mortality (1, 2), and this joins an ever-growing body of international and national guidelines on hyponatraemia. This includes the international expert panel recommendations by Verbalis *et al.* (3), and various national recommendations from Spain (4), Sweden (5) and the UK (6). The development of hyponatraemia guidelines in Italy and Norway is also ongoing.

Therefore, it seems to be unusual that tolvaptan, the only licensed vasopressin receptor antagonist (vaptan) for hyponatraemia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1, 2), has been excluded from the European 'Clinical Practice Guideline on the diagnostic approach and treatment of hyponatraemia' (1, 2). By contrast, most of the recommended treatments are unlicensed for treating the conditions that they are recommended for and do not have the benefit–risk assessment that is signified by licence approval following the regulatory assessment by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) (7, 8).

Notably, some of the recommendations of the ERBP guideline are in contrast to those of the other publications mentioned above, particularly in patients with SIADH (1, 2, 3, 4, 5, 6).

Unusually, the authors have chosen to analyse four vaptans (tolvaptan, conivaptan, lixivaptan and sata-vaptan) within the same meta-analysis (9, 10) when only tolvaptan is licensed and approved for use in Europe (1, 2). Moreover, this analysis is based on a heterogeneous population that includes hypervolaemic patients, whereas in Europe tolvaptan is authorised for use only in patients with euvolaemic hyponatraemia secondary to SIADH (1, 2, 9, 10).

Although there is a paucity of evidence to support evidence-based recommendations for most available therapies in hyponatraemia (3), the efficacy and safety profile of tolvaptan have been proven in randomised controlled trials (11). Furthermore, since 31 March 2013, pooled exposure data have been made available for the ongoing evaluation of safety from 82 trials, including 6794 subjects worldwide who were exposed to oral doses of tolvaptan, with 425 subjects in trials for hyponatraemia (12). Therefore, it is surprising that the European guideline does not recommend a place for tolvaptan within its licensed indication (1, 2). Based on their review of a meta-analysis consisting predominantly of unlicensed vaptans, the authors concluded that the benefit–risk profile for vaptans seems to be negative. Vaptans, similar to all other treatments for hyponatraemia, can occasionally cause overly rapid correction of hyponatraemia (11). A single case of osmotic demyelination syndrome (13), with a very rare incidence of less than one in 10 000 patients, has been reported with tolvaptan monotherapy to date. The summary of product characteristics for tolvaptan emphasises the importance of close monitoring of serum sodium concentration and titrating the dose to achieve a desired serum sodium concentration in all patients (7).

The authors also expressed concern with the hepatotoxicity associated with the use of particularly high doses of tolvaptan in autosomal dominant polycystic kidney disease (ADPKD) (1, 2). However, there have been no liver safety signals to date in any other population treated with tolvaptan (hyponatraemia, heart failure or cirrhosis) (14). The long-term safety profile of tolvaptan has been confirmed in the SALTWATER study, with a mean duration of treatment of 1.9 years (15).

The vaptan meta-analysis also suggested a signal indicating a possibly increased risk of death for

hypervolaemic patients treated with vaptans compared with placebo (1, 2). Moreover, it is important to note that in Europe tolvaptan is not approved in this patient population (1, 2) and there was no increase in mortality when the tolvaptan subgroup was analysed (9, 10).

With the rigour afforded to the analyses of the risk-benefit profile for vaptans, it is surprising that the same in-depth analyses do not seem to have been conducted for any treatments the ERBP guideline recommends for SIADH. The authors acknowledge that there are no systematic reviews or randomised controlled trials evaluating the benefits and harms of fluid restriction, urea or loop diuretics (1, 2).

Yet the authors' recommendation for first-line treatment with fluid restriction fails to acknowledge that it may be inappropriate for many patient populations (e.g. in patients with cancer where it may delay chemotherapy (16, 17), and it is likely to fail in some patients (e.g. those with high urine osmolality) (3).

The guideline recommends second-line treatment with urea or the combination of loop diuretics with oral sodium chloride (NaCl), despite extremely limited efficacy data (1, 2). The authors failed to consider safety data for the use of urea in the studies they quote, for example, one study has shown that urea is associated with a 37% rate of overly rapid correction in patients with severe hyponatraemia (18). In addition, of the four studies mentioned supporting the use of loop diuretics with oral NaCl (19, 20, 21, 22), only one study actually used oral NaCl ( $n=9$ ), with the remaining studies using NaCl intravenously (19). There is no discussion on the rationale for the inclusion of this combination or any consideration of safety data (1, 2), for example, overly rapid correction was observed in 56–80% of patients in two case series (20, 22), and hypokalaemia developed in 58% of patients in another study (19).

Tolvaptan has a proven benefit–risk profile, which is supported by randomised controlled trials and over 4 years of real-world use, and we urge the authors to take a more consistent and measured approach towards evidence-based recommendations.

## Reply to this letter

A response to this letter (23) is being published in this issue.

### Declaration of interest

The author is currently Regional Vice President, Medical Europe for Otsuka Pharmaceutical Europe Ltd.

### Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

### Co-publication

This letter will be co-published in the *European Journal of Endocrinology* and *Nephrology Dialysis Transplantation*.

## References

- Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *European Journal of Endocrinology* 2014 **170** G1–G47. (doi:10.1530/EJE-13-1020)
- Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrology, Dialysis, Transplantation* 2014 **29** (Suppl 2) i1–i39. (doi:10.1093/ndt/gfu040)
- Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH & Thompson CJ. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *American Journal of Medicine* 2013 **126** S1–S42. (doi:10.1016/j.amjmed.2013.07.006)
- Runkle I, Navarro A, Pose A, Villabona C, Formiga F, Tejedor A & Poch E. El tratamiento de la hiponatremia secundaria al síndrome de secreción inadecuada de la hormona antidiurética. *Medicina Clínica* 2013 **141** 507.e1–507.e10. (doi:10.1016/j.medcl.2013.09.002)
- Chantzichristos D, Drougge H, Dahm P, Edén Engström B, Ekman B, Höybye C, Manhem P, Olsson T, Rask E, Öhlin B & Johannsson G. Vårdprogram för hyponatremi. Gothenburg, Sweden: Svensk Förening för Anestesi och Intensivvård & Svenska Endokrinolog Föreningen; 2012. Available at: [http://endokrinologforeningen.se/documents/Svenskt%20vardprograQ7m%20for%20hyponatremi\\_120120.pdf](http://endokrinologforeningen.se/documents/Svenskt%20vardprograQ7m%20for%20hyponatremi_120120.pdf)
- Grossman A, Thatcher N, Bouloux P, Grant P, Cohen M, Murray R, Rees A, Ayuk J & Cranston I. Expert Panel Guidelines for the Treatment of Hyponatraemia (Draft version, presented at Stratford, UK, February 7th–8th 2013).
- Otsuka Pharmaceutical Europe Ltd. Samsca (tolvaptan) summary of product characteristics. European Medicines Agency; 2014.
- Otsuka America Pharmaceutical, Inc. Samsca (tolvaptan) prescribing information 2014.
- Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn EJ, Ichai C *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrology, Dialysis, Transplantation* 2014 **29** (10 Suppl 2) i1–i39. Supplementary appendix 6. (doi:10.1093/ndt/gfu040)
- Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C *et al.* Clinical practice guideline on diagnosis and treatment of hyponatraemia. *European Journal of Endocrinology* 2014 **170** G1–G47. Supplementary appendix 6. (doi:10.1530/EJE-13-1020)
- Verbalis JG, Adler S, Schrier RW, Berl T, Zhao Q, Czerwiec FS & SALT Investigators. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *European Journal of Endocrinology* 2011 **164** 725–732. (doi:10.1530/EJE-10-1078)

- 12 Otsuka Pharmaceutical Europe Ltd. Tolvaptan pooled exposure data. Data on file: Periodic Update Safety Report July 2013. Wexham, Bucks, UK; Otsuka Pharmaceutical Europe Ltd: 2013.
- 13 Malhotra I, Gopinath S, Janga KC, Greenberg S, Sharma SK & Tarkovsky R. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. *Case Reports in Endocrinology* 2014. (doi:10.1155/2014/807054)
- 14 Otsuka Pharmaceutical Europe Ltd. Tolvaptan liver safety data. Data on file. Wexham, Bucks, UK; Otsuka Pharmaceutical Europe Ltd: 2014.
- 15 Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS & SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. *Journal of the American Society of Nephrology* 2010 **21** 705–712. (doi:10.1681/ASN.2009080857)
- 16 Rosner MH & Dalkin AC. Electrolyte disorders associated with cancer. *Advances in Chronic Kidney Disease* 2014 **21** 7–17. (doi:10.1053/j.ackd.2013.05.005)
- 17 Castillo JJ, Vincent M & Justice E. Diagnosis and management of hyponatremia in cancer patients. *Oncologist* 2012 **17** 756–765. (doi:10.1634/theoncologist.2011-0400)
- 18 Decaux G, Andres C, Gankam-Kengne F & Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Critical Care* 2010 **14** R184. (doi:10.1186/cc9292)
- 19 Decaux G. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by long loop diuretics. *Nephron* 1983 **35** 82–88. (doi:10.1159/000183052)
- 20 Forssell G, Nordlander R & Orinius E. Treatment of dilutional hyponatremia in congestive heart failure. *Acta Medica Scandinavica* 1980 **207** 279–281. (doi:10.1111/j.0954-6820.1980.tb09721.x)
- 21 Castello L, Pirisi M, Sainaghi PP & Bartoli E. Quantitative treatment of the hyponatremia of cirrhosis. *Digestive and Liver Disease* 2005 **37** 176–180. (doi:10.1016/j.dld.2004.10.008)
- 22 Hantman D, Rossier B, Zohlman R & Schrier R. Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. An alternative treatment to hypertonic saline. *Annals of Internal Medicine* 1973 **78** 870–875. (doi:10.7326/0003-4819-78-6-870)
- 23 Van Biesen W & Vanholder R. Clinical Practice Guideline on diagnosis and treatment of hyponatraemia: a response to letter from Otsuka Ltd. *European Journal of Endocrinology* 2014 **171** L5. (doi:10.1530/EJE-14-0393)

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Received 15 May 2014

Revised version received 15 May 2014